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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,739	03/14/2002	Masayuki Amagai	201487/1070	5390

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EXAMINER	
LI, QIAN J	JD

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,739	AMAGAI ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 2-25 are pending in the application and under current examination. In the preliminary amendment, claim 1 has been cancelled, claims 2-4, 6, 7, 9, 14, 15, and 17 have been amended, and claims 19-25 are newly submitted.

Priority

This application is a 371 application of PCT/JP00/02023, filed 3/30/2000; and claims benefit of priority from JP11/91408, filed 3/31/1999.

Claim Objections

Claims 2, 3, and 11 are objected to because of the following informalities: an article should precede "autoimmune" in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a mouse model showing a phenotype of pemphigus vulgaris by transplanting *activated* immune cells into an *immunodeficient* mouse, wherein said activated immune cells are obtained by immunizing a Dsg3-/-

mouse lacking a Dsg3 (desmoglein 3) antigen with said Dsg3 antigen, does not reasonably provide enablement for making *any* non-human mammal showing a phenotype of any autoimmune disease, and it does not reasonably provide enablement for making a non-human PV model/any non-human autoimmune model by transplanting *non*-activated immune cells, or by transplanting activated immune cells into an *immune competent* non-human mammal, or by transplanting activated immune cells to a *xenogenic* immunodeficiant non-human mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claim 2 is drawn to a non-human mammal showing a phenotype of an autoimmune disease, wherein the disease is induced by transplanting immune cells from a non-human mammal lacking an antigen gene, which antigen is responsible for

the autoimmune disease. Given the broadest reasonable interpretation, the claim does not require the donor non-human mammal lacking the antigen gene being immunized with the antigen before obtaining the immune cells for transplantation. However, according to the common knowledge in the art, the immune cells obtained from an non-immunized donor mammal lacking the antigen gene would not and could not have the capability to react with the antigen in a recipient because the immune cells have never exposed and activated by the antigen, consequently, the recipient non-human mammal would not have a phenotype of the autoimmune disease associated with the antigen. Therefore, claim 2 and dependent claims do not appear to be enabled in the absence of evidence to the contrary.

Given the broadest reasonable interpretation, claims 2, 3, and 11 encompass transplanting immune cells between immune competent non-human mammals, and between different species or different individuals within the same species. According to the common knowledge in the art, such transplantation would trigger an allogenic or xenogenic transplantation rejection response. The vigorous rejection response may be detrimental to the recipient mammal before any phenotype of an autoimmune disease appears, and may override the autoimmune response by eliminating the transplanted immune cells. Therefore, the claims do not appear to be enabled in the absence of evidence to the contrary.

Moreover, when transplanting immune cells from a xenogenic source, for example, from a knockout mouse to a primate, even if the recipient primate is immunodeficient, a phenotype of autoimmune disease may not show because the

autoantibody to a mouse antigen may not be cross-reactive to a primate's antigen. This is evidenced by the teaching of *Juhasz et al* (J Clin Invest 1993;92:2401-7, IDS). *Juhasz et al* teach transferring peripheral blood lymphocytes of patients with pemphigus vulgaris to SCID mice. Although circulating anti-pemphigus antibodies were found in 20 of the 34 successfully reconstituted mice, and 44% of the mice had deposits of human IgG in their own skin, spontaneous PV-like blisters were rarely found in mouse skin. In the contrast, the Pemphigus Vulgaris-like lesions developed in human skin grafts within the host SCID mouse (abstract). Therefore, the claims do not appear to be enabled in the absence of evidence to the contrary.

The claimed method for producing a non-human mammal showing a phenotype of an autoimmune disease requires transplanting immune cells from an immunized donor non-human mammal that lacks an antigen gene associated with the autoimmune disease into a recipient immunodeficient non-human mammal. It is noted that it is well known in the art to establish an animal model for a human disease by immunizing a donor animal with a particular autoantigen and adoptively transferring the immune cells from the immunized animal to an immunodeficient animal, or adoptive transferring the immune cells of a subject with a pre-existing autoimmune disease to an immune deficient animal, preferably with a target tissue of the subject. However, the prior art fails to teach immunizing, with an antigen, a non-human mammal lacking the antigen, specifically a knockout mouse as taught in the specification, and using the activated immune cells from the knockout mouse as donor immune cells. Accordingly, practicing the present invention requires using a complete line of non-human mammals deficient in

a particular antigen associated with a particular autoimmune disease, particularly an antigen knock out non-human mammal. The specification teaches that Dsg3 is the causative antigen for pemphigus vulgaris, and the Dsg3 knockout mice were used for immunization. However, the specification fails to teach any other antigen knockout animal besides Dsg3-/- and whether such practice could be reasonably extrapolated and applied to any autoimmune disease model. In view of the state of the art in autoimmunity, autoantigens responsible for a particular disease is either not clearly defined or not limited to one particular protein. For example, autoantibodies of systemic lupus erythematosus (SLE) are against ubiquitous and abundant intracellular antigens, such as chromatin, it is impossible to raise a mammal without the chromatin. In insulin-dependent diabetes (IDDM), cytotoxic T cells target multiple surface proteins and products of pancreatic islet cells, such as insulin, GAD, and LA-2, it is impractical to generate a non-human mammal without islet cells or insulin since they are vital for metabolism; in autoimmune hemolytic anemia, autoantigens are clustered on the surface of red blood cells, it is unfeasible to generate a non-human mammal without red blood cells. (*Janeways Jr.*, Immunobiology, 5th Edition, c2001, Sections 13-4 to 13-7, and *Bach et al*, IDS). Even if the antigen is known and limited to a particular cellular receptor, such as AchR for myathesnia gravis, and GpIIb:IIIa fibrinogen receptor for autoimmune thrombocytopenic purpura, the physiological consequence of knocking out the receptors and viability of the resulting mammals are unpredictable. Although the specification outlines the principle of the invention, it fails to teach beyond the Dsg3-/- mouse, which autoantigen could be knocked out homozygously while the mammal

could survive and serve as the donor of immune cells. Therefore, the specification fails to provide an enabling disclosure to guide the practice of the invention commensurate with the scope of the claims.

Practicing the claimed invention requires making a line of transgenic non-human mammals. Although the techniques of making transgenic and knock out animals have become routine in the relevant art, the resulting genotype and phenotype vary significantly depending on the genes being manipulated, and the animals being used. For example, the instant specification teaches that in order to induce autoimmune pemphius vulgaris, the immune cells from a homozygous Dsg3-/-, but not heterozygous Dsg3+/- mouse, must be used. With regard to homozygous knock out, *Yamamura* (Prog Exp Tumor Res Basel, Karger, 1999;35:13-24) teaches that gene manipulation and the resulting phenotype of transgenic animals is not always consistent due to reasons such as gene functional redundancy and species difference, and that homozygous transgenic animal may not be viable. "THE LOSS OF FUNCTION OF *RB* IS ASSOCIATED WITH AN INHERITED GENETIC PREDISPOSITION TO RETINOBLASTOMA", "HOMOZYGOUS MICE, TOTALLY DEFICIENT OF *RB*, ARE NONVIABLE DUE TO DEFECTS IN NEUROGENESIS AND HEMATOPOIESIS AND THEREFORE ARE NOT USEFUL AS MODELS FOR CANCER RESEARCH".

With regard to creating transgenic/knockout non-human mammals across board, without evidence to the contrary, transgene expression and knockout phenotype in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is supported by *Mullins et al.*(J Clin Invest 1996 Apr;97:1557-60), and *Linder* (Lab Animal 2001 May;30:34-9). *Mullins et al* state "A

GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER" (page 1559, Summary). *Linder* (Lab Animal 2001 May;30:34-9) teaches "THE GENETIC BACKGROUND AND THE SURROUNDING ENVIRONMENT ARE OFTEN OVERLOOKED PARAMETERS THAT CAN SIGNIFICANTLY AFFECT THE OBSERVED PHENOTYPE", "OTHER FACTORS INCLUDE MUTATIONS THAT ARE ACTUALLY HYPOMORPHS (I.E. MUTATIONS THAT CAUSE ONLY A PARTIAL DECREASE IN GENE EXPRESSION) RATHER THAN NULL ALLELES; COMPENSATORY PATHWAYS; AND TRANSGENESIS-SPECIFIC FACTORS, INCLUDING SITE OF INTEGRATION, TRANSGENE COPY NUMBER, AND INSERTIONAL MUTATIONS", "GENETIC BACKGROUND IS DEFINED AS A COLLECTION OF ALL GENES PRESENT IN AN ORGANISM THAT INFLUENCE A TRAIT OR TRAITS. WHILE MOST OF THE COMMONLY USED INBRED STRAINS SHARE A FAIRLY COMMON ORIGIN, EACH STRAIN HAS ITS OWN UNIQUE SET OF CHARACTERISTICS OR BACKGROUND LESIONS", "THE PHENOTYPE OF MICE CARRYING A MODIFIED GENE WILL VARY DEPENDING ON THE GENETIC BACKGROUND BECAUSE OF THE PRESENCE OF GENETIC MODIFIERS (ALLELIC VARIANTS AT LOCI OTHER THAN THE ONE BEING GENETICALLY MODIFIED) IN THE INBRED STRAIN GENOME" (see entire article). Thus, the phenotypes resulting from targeted disruption of an antigenic gene in different strains are expected to be varied and unpredictable.

Logan and Sharma (Clin Exp Pharmacol Physiol 1999 Dec;26:1020-25) teach "THE CHALLENGE IN THE DEVELOPMENT OF TRANSGENE IS NOT IN THIS PROCESS, BUT IN THE DESIGN OF THE CONSTRUCT THAT WILL ALLOW FOR THE EXPRESSION OF THE GENE OF INTEREST IN THE DESIRED CELL TYPE AT AN APPROPRIATE LEVEL", "PROBLEMS WITH OBTAINING EXPRESSION OF TRANSGENES IN ANIMALS HAVE BEEN RELATED TO THE INABILITY TO ROUTINELY OBTAIN HIGH LEVELS OF EXPRESSION, ESPECIALLY OVER MULTIPLE GENERATIONS, AND THE OBSERVATION OF VARIEGATED EXPRESSION, WHEREBY NOT ALL CELLS IN AN ORGAN WILL EXPRESS THE GENE. Thus, the phenotypes resulting from homozygous knock out of a particular antigen are expected

to be varied and unpredictable. The skilled artisan could not practice the invention without first carrying out undue experimentation to make a homozygous knockout for a particular gene.

Thus, it is evident that at the time of the invention, the skilled artisan, while acknowledging the significant potential of transgenic technology, still recognized that making a transgenic animal with desired phenotype was neither routine nor accepted, and awaited specific guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for making and using the complete line of non-human mammals lacking an antigen gene. Although the instant specification provides an example for pemphigus vulgaris, it is not enabled for making and using any and all non-human mammals lacking an antigen, and it is not enabled for making the mammal with the method as it is broadly claimed. Accordingly, in view of the quantity of experimentation necessary to make a non-human mammal lacking an antigen for an autoimmune disease and immune competent, the lack of guidance provided by the specification as well as the absence of working examples with regard to *any* and *all* of non-human mammals for any type of autoimmune diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite because claim 2 recites the limitation "the non-human mammal" in line 4. Two different types of non-human mammals are recited in line 1 and line 3, it is unclear which non-human mammal the phrase in line 4 refers to since the immune cells could be transplanted back to the mammal, and thus the metes and bounds of the claim are unclear. Likewise, the dependent claims of claim 2 begin with, "the non-human mammal of claim...", they should be amended to recite the particular mammal the claim recitation refers to.

Claim 3 is vague and indefinite because claim 3 recites the limitation "the non-human mammal" in line 5. Two different types of non-human mammals are recited in line 1 and line 3, it is unclear which non-human mammal the phrase in line 5 refers to since the immune cells could be transplanted back to the mammal, and thus the metes and bounds of the claim are unclear. Likewise, the dependent claims of claim 3 begin with, "the non-human mammal of claim...", they should be amended to recite the particular mammal the claim recitation refers to.

Claims 2 and 3 are vague and indefinite because of the claim recitation, "T cell activation". This is because it is unclear which phrase of the claim is the alternative for "T cell activation" in line 3, in another word, which preposition it should follow, e.g. "through", "of", or "for", thus, the metes and bounds of the claims are unclear.

Claims 2, 3, and 11 are vague and indefinite because of the phrase, "through production of an antibody...", it is unclear how the antibody is produced, and whether the phrase is a step of the method process or an adjective defining the nature of the autoimmune disease, thus, the metes and bounds of the claims are unclear.

Claims 2, 3, and 11 are vague and indefinite because of the claim recitation, "T cell activation". Assuming applicants intend to recite, "an autoimmune disease through T cell activation", it is unclear how T cell activation is associated with an autoimmune disease, and whether the phrase is a stem of the method process. According to the common knowledge in the art, not all T cell activation would cause an autoimmune disease; only the activation of T cells specifically reactive to auto-antigens would lead to an autoimmune disease.

Claim 9 is vague and indefinite because of the claim recitation, "wherein the non-human mammal". Two different types of non-human mammals are recited in claim 2 from which claim 9 depends, it is unclear which non-human mammal the phrase in claim 9 refers to, and thus the metes and bounds of the claim are unclear.

Claim 11 is vague and indefinite because it is incomplete. The method provides for producing a non-human mammal showing a phenotype of an autoimmune disease, however, the claim does not recite a positive step or conclusion that clearly relates back to the preamble.

Claim 17 is vague and indefinite because of the claim recitation, "the non-human mammal". Two different types of non-human mammals are recited in claim 11 from

which claim 17 depends, it is unclear which non-human mammal the phrase in claim 17 refers to, and thus the metes and bounds of the claim are unclear.

Claim 24 is vague and indefinite because of the claim recitation, "wherein the non-human mammal". Two different types of non-human mammals are recited in claim 3 from which claim 24 depends, it is unclear which non-human mammal the phrase in claim 24 refers to, and thus the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2-25 are rejected under 35 U.S.C. 102(a) as being anticipated by *Amagai et al* (J Clin Invest 2000 Mar 1;105:625-31, IDS).

Claims 2-10, and 19-25 are drawn to a non-human mammal showing a phenotype of an autoimmune disease, wherein immune cells from a donor non-human mammal lacking an antigen gene have been transplanted to a recipient non-human mammal, preferably the recipient mammal is a rodent, an immunodeficient mouse such as RAG2 transgenic mouse, wherein the immune cells are splenocytes, wherein the antigen is Dsg3, and the autoimmune disease is pemphigus vulgaris. Claims 11-18 are drawn to a method of making the non-human mammal showing a phenotype of autoimmune disease.

Amagai et al teach a non-human mammal, particularly an immunodeficient Rag-/- mouse, showing a phenotype of pemphigus, an autoantibody mediated autoimmune disease, wherein the Rag-/- mouse received splenocytes from Dsg3-/- mice immunized with Dsg3 protein, wherein the recipient mice developed the phenotype of PV (abstract, figs. 3-4). Therefore, *Amagai et al* anticipate instant claims.

Please note that the reference applies as prior art because it has a different inventive entity with instant applicant; and applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-

1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
March 24, 2003